Interim Update: Newborn Screening for Krabbe Disease for the 2022 RUSP Nomination

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Robert T. Stone, MD	University of Rochester	Clinician Scientist
Jacque Waggoner	Hunter's Hope Foundation	CEO

Expert Calls and Interviews

- TEP Call #1: August 8, 2022
- TEP Call #2: September 30, 2022
- Additional Key-Informant Interviews
  - Dr. Robert Stone: August 29, 2022
  - Dr. Jennifer Kwon: September 8, 2022
  - Dr. Samantha Vergano: September 9, 2022
  - Dr. Maria Escolar: September 12, 2022
  - Dr. Laura Feltri: September 21, 2022
  - Stacy Pike-Lagenfeld and Ann Rugari: October 19, 2022

Outline

- Overview
- Current Progress
- Next Steps

Krabbe Disease: 2009 ACHDNC Review

- Not recommended for the RUSP
- Gaps identified by the Advisory Committee include
  - Definition of early infantile Krabbe Disease (EIKD)
  - Screening and treatment algorithm for EIKD
  - Benefit of hematopoietic stem cell transplant (HSCT), including whether specific variants would most benefit
  - Concern about over-referral and potentially burdensome follow-up
- Advancements since 2009 include psychosine testing, which can decrease false positive referrals

Krabbe Disease

- Reported birth prevalence:~1 per 100,000
  - Range from 1 in 394,000 to 1 in 12,080 based on a range of different study types
- Lysosomal storage disorder and leukodystrophy
- Chromosome 14 (autosomal recessive)
  - >200 *GALC* variants, many private and not all pathogenic
  - Some specific variants are predictive of outcomes
- Low galactocerebrosidase (GALC) enzyme activity
- Elevated psychosine concentration in early infancy

Krabbe Disease: Natural History

Bascou N et al. A prospective natural history study of Krabbe disease in a patient cohort with onset between 6 months and 3 years of life. *Orphanet J Rare Dis.* 2018;13:126.
Komatsuzaki S, et al. Clinical characteristics of 248 patients with Krabbe disease: quantitative natural history modeling based on published cases. *Genet Med.* 2019;21:2208-2215.
Krieg et al. Natural history of Krabbe disease -- a nationwide study in Germany using clinical and MRI data. *Orphanet J Rare Dis.* 2015;15:243.

- For those who develop symptoms <6 months
  - Present on average at about 4 months
  - About half develop head control, but lose it within 2 months
  - Spasticity an early finding
  - Early onset of severe irritability
  - Significant swallowing problems by 4 months
  - Loss of fixation by 4.5 months
  - Most will not develop any language
  - Loss of vision and hearing
  - Seizures (variable onset)
  - Survival to 10-32 months
- For those who develop symptoms from 6-36 months
  - Present with irritability and developmental regression, with milestone loss, around 14-16 months
  - Median survival 6.7 years

Infantile Krabbe Disease

- Evolution of classification, reflecting different epidemiological and clinical uses
- Nominated condition includes cases with onset ≤36 months, but evidence review will also include reported cases with later-onset Krabbe disease.

ONSET of symptoms
Escolar et al. 2017
- Early Infantile: < 6 mo
- Late infantile: 6-48 mo
- Juvenile: 4-8 yrs

ONSET of symptoms
Wenger et al. 2019
- Infantile: < 6 mo
- Late-onset:
  - Late infantile: 6-36 mo
  - Juvenile: 3-8 years

ONSET of symptoms
Thompson-Stone, 2021
- Early Infantile: < 6 mo
- Late infantile: 6-12 mo
- Late-onset: early childhood and adolescents/adults

Approach to Screening

- Tier 1: Dried-blood spot GALC enzyme activity
- Additional Testing:
  - Dried-blood spot psychosine
    - Reduces false positives
    - Helps to stratify risk
  - Molecular analysis
    - Can identify variants with known severity

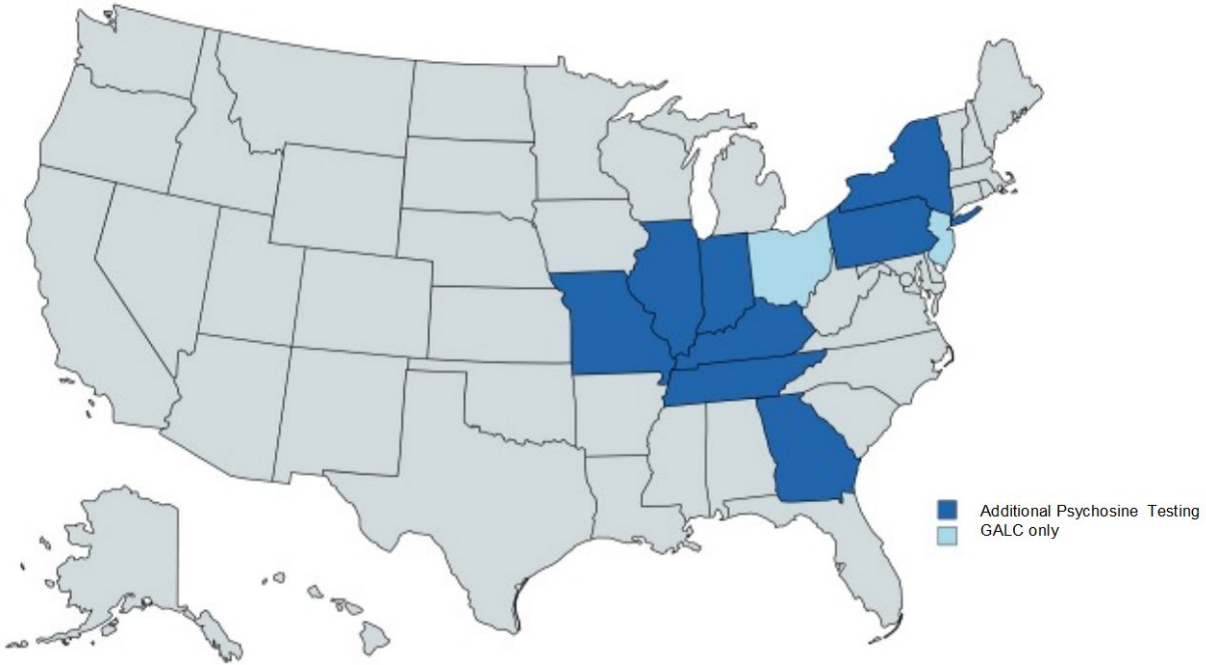
Expert Panel Recommendations For Follow-up After a Positive Newborn Screen

Thompson-Stone R, Ream MA, Gelb M, et al. Consensus recommendations for the classification and long-term follow up of infants who screen positive for Krabbe disease. *Mol Genet Metab*. 2021;134:53-59.

- Dried-blood spot psychosine levels
  - ≥2 nmol/L abnormal
    - ≥10 nmol/L strongly predictive of early infantile Krabbe disease and follow-up is time critical
- Three pathways
  - Early Infantile: immediate referral for diagnostic evaluation and treatment
  - "At-risk for late-onset Krabbe disease" (late infantile, childhood, juvenile, adult onset): follow-up in 2-4 weeks by a specialist or primary care provider in consultation with a specialist for further testing. Genotype can further stratify infants to:
    - High risk: Specialty visits every 2-3 months for 24 months, every 6 months until 3 years, annually until 12 years, 2-5 years until adulthood
    - Low risk: Specialty visits every 6 months for 24 months, annually until 12 years, 2-5 years until adulthood
  - Not expected to have Krabbe disease: no follow-up
- Using psychosine this way reduces referral from newborn screening

State Newborn Screening Programs that include Krabbe Disease

- Georgia
- Indiana
- Illinois
- Kentucky
- Missouri
- New Jersey
- New York
- Ohio
- Pennsylvania
- Tennessee



New York Krabbe Disease Newborn Screening: First 8 years

Orsini, J. J., Kay, D. M., Saavedra-Matiz, C. A. et al. Newborn screening for Krabbe disease in New York State: the first eight years' experience. *Genet Med.* 2016;1*8:*239–248.

- Krabbe Disease screening 2006 through 7 August 2014
- 2,090,910 specimens, 1,968,568 infants
- **2-tier screening**
  - GALC activity (≤12%) n=620
  - molecular GALC analysis n=348 referred for follow-up
    n=272 GALC polymorphisms only (neg screen)
- **Diagnostic testing (n=348)**

	n	%
Lost to follow-up	2	<0.001%
No risk	203	0.01%
Low risk	92	0.004%
Moderate risk	37	0.002%
High risk	9	<0.001%
High risk: confirmed infantile KD	5	<0.001%

Illinois Krabbe Disease Newborn Screening

Basheeruddin et al. Newborn Screening for Krabbe Disease—Illinois Experience: Role of Psychosine in Diagnosis of the Disease the first eight years' experience. I*nt J Neonatal Screen.* 2021:7;24.

- Dec 2017 to Dec 2020
- 497,147 infants screened
- Two-tier screening
  - GALC activity (≤16%) n=838
  - Repeat GALC (≤ 13%) n=288

  2nd tier

  a) psychosine levels

  b) GALC sequencing
- 2 newborns with elevated psychosine levels (10 and 35), referred immediately
- 6 newborns with psychosine levels 2-5
- 178 with pseudodeficiency alleles (psychosine <2)

Preliminary Data: Krabbe Disease Newborn Screening, Incorporating Psychosine Testing

State	Years	Number of Infants Screened	Referrals (per 100,000 screened)	Infantile KD* (per 100,000 infants)	"At Risk" for Late-Onset KD* (per 100,000 screened)
Georgia	2021-2022	144,000	0.7	0.7	0
Illinois	2021-2022	98,721	8.1	0	2.0
Indiana	2020-2022	172,803	6.4	0	2.3
Kentucky	2016-2022	330,555	0.6	0.6	0
Missouri	2020-2022	168,042	11.9	0.6	1.2
Pennsylvania	2021-2022	167,537	11.3	1.8	0.6
Tennessee	2017-2022	421,481	13.8	0.2	0.5

- Some newborn screening programs refer based on GALC enzyme activity or molecular testing results prior to the availability of psychosine level

Diagnostic Evaluation

- GALC enzyme activity (clinical), psychosine concentration (clinical), molecular testing (if not previously done)
- Additional information, may be done in conjunction with planning for HSCT to minimize delay
  - MRI
  - Nerve conduction studies
  - Electroencephalogram (EEG)
  - Auditory and Visual Evoked Potentials
  - Cerebrospinal fluid (CSF) protein

Treatments

Thompson-Stone R, Ream MA, Gelb M, et al. Consensus recommendations for the classification and long-term follow up of infants who screen positive for Krabbe disease. *Mol Genet Metab*. 2021;134:53-59.
Kwon JM, Matern D, Kurtzberg et al. Concensus guidelines for newborn screening, diagnosis and treatment of infantile Krabbe disease. *Orph J Rare Diseases*. 2018;13:30.

- HSCT
  - Presumed early infantile Krabbe Disease: urgent referral with the goal of transplant by 30 days (ideally)
  - Later HSCT for other phenotypes, following the development of signs or symptoms
- Gene therapy being evaluated in clinical trials

HSCT Outcomes By Timing of Treatment

Allewelt H, Taskindoust M, Troy J et al. Long-Term Functional Outcomes after Hematopoietic Stem Cell Transplant for Early Infantile Krabbe Disease. Biol Blood Marrow Transplant. 2018; 24: 2233-2238.

- 19 subjects with HSCT for early infantile Krabbe disease by 2 months of age between 1996-2010 in a single center, with at least 5 years of follow-up
  - Diagnosed through newborn screening (16%) or family history (84%)
  - Median age of transplant: 27 days (range 19-61 days)
  - Most (18/19) treated with umbilical cord blood from unrelated donors
  - Survival at 5 years: 84%, at 10 years: 79%
  - No differences in 5- or 10-year survival by HSCT <30 days (n=17) vs. HSCT ≥30 days (n=7)
  - Other outcomes after 5 years post-HSCT

Other functional outcomes	Transplant <30 days	Transplant ≥30 days	Statistical significance
Walking +/- device	90%	17%	p=0.01
Communication (“verbal”)	100%	50%	p=0.02
Feeding by mouth	90%	17%	p=0.008
Seizures	0%	33%	NS

New York Krabbe Disease Newborn Screening Outcomes (2016)

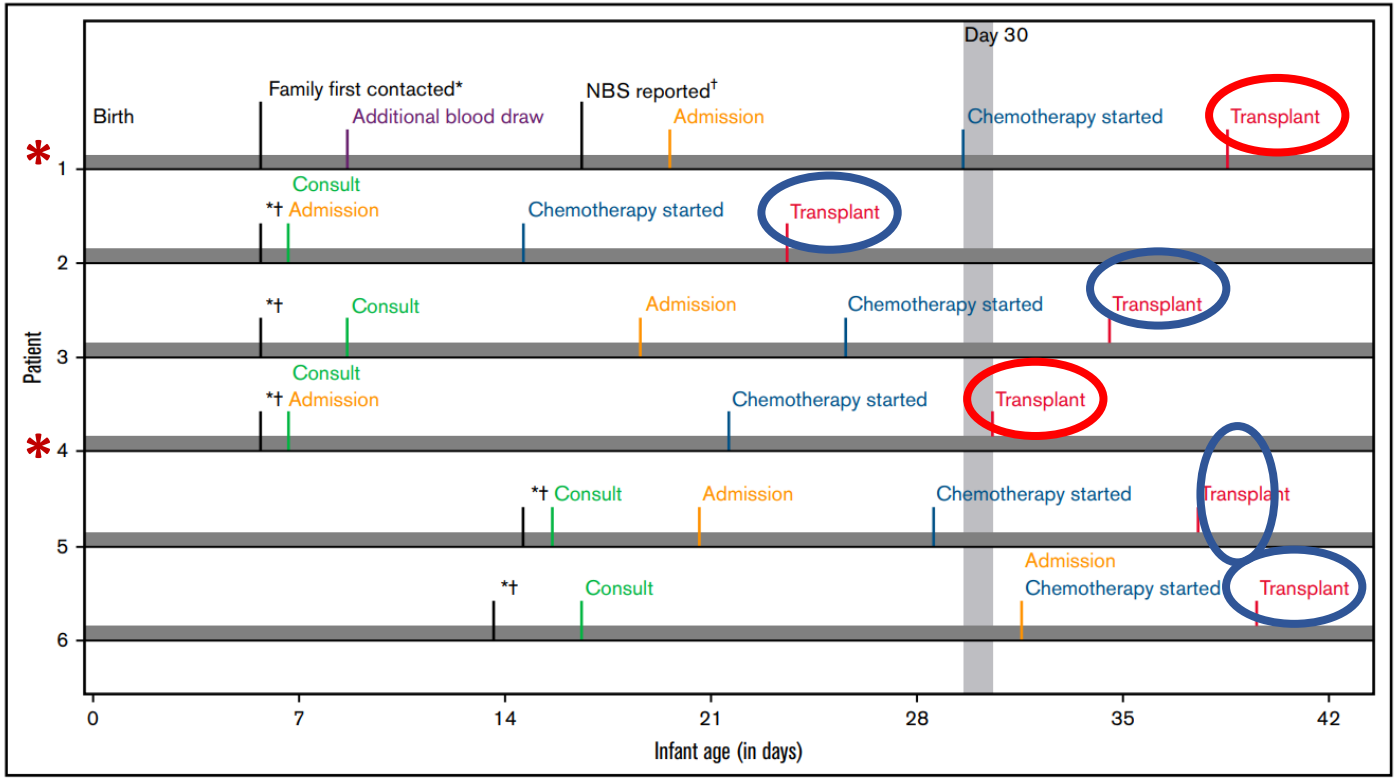
Wasserstein et al. 2016. Clinical outcomes of children with abnormal newborn screening results for Krabbe disease in New York State. *Genet Med.* 2016;18(12): 1235-1243.

- ~2 million screened
- 348 newborns referred, with 2 lost to follow-up
  - 5 with early infantile Krabbe disease, 4 treated with HSCT

HSCT	Age at follow up	Complications or cause of death
24 days	Death at 69 days	Pulmonary hypertension
31 days	Death at 84 days	HSCT-related complications
32 days	8 years	Developmental delay, non-ambulatory. Post-HSCT course complicated by autoimmune hemolytic anemia and hypertrophic cardiomyopathy
41 days	5 years	Developmental delay and failure to thrive
Refused	Death at 18 months	Krabbe disease

Newborn Screening Krabbe Disease Treatment after NBS in IL, KY, MO, OH

Page K, Ream MA, Rangarajan HG, et al. Benefits of newborn screening and hematopoietic cell transplant in infantile Krabbe disease. Blood Adv. 2022; 6:2947-2956.

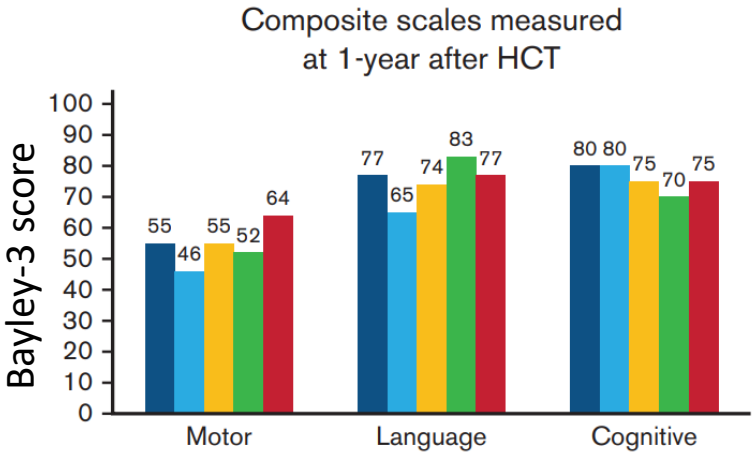


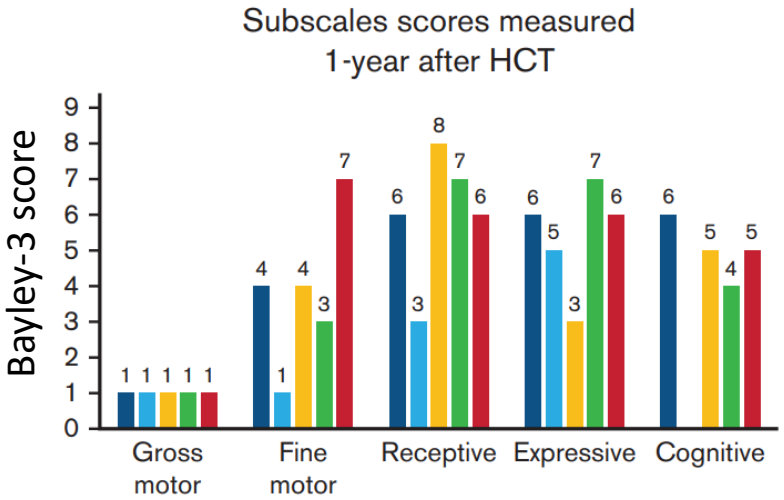
*HSCT out of state

Newborn Screening Treatment Outcomes

Page K, Ream MA, Rangarajan HG, et al. Benefits of newborn screening and hematopoietic cell transplant in infantile Krabbe disease. Blood Adv. 2022; 6:2947-2956.

- Neurologic evaluations for 5 children alive 30-58 months after HSCT, all with developmental delays (particularly related to gross motor deficits)





Ongoing focus

- Screening results
- Outcomes of HSCT for those with early identification
  - Where possible, stratify by genotype and initial GALC enzyme activity and psychosine level

Projecting Population Health Outcomes

Using modeling, objective is to project population-level health outcomes

- Annual US newborn cohort of 3.65 million
- Health outcomes
  - Newborn screening
    - Screening outcomes (positive screens, confirmed Krabbe disease, at risk, etc)
    - Numbers of babies who receive transplant, projected transplant outcomes
    - Mortality
  - Clinical Identification
    - Identified cases of Krabbe disease
    - Mortality

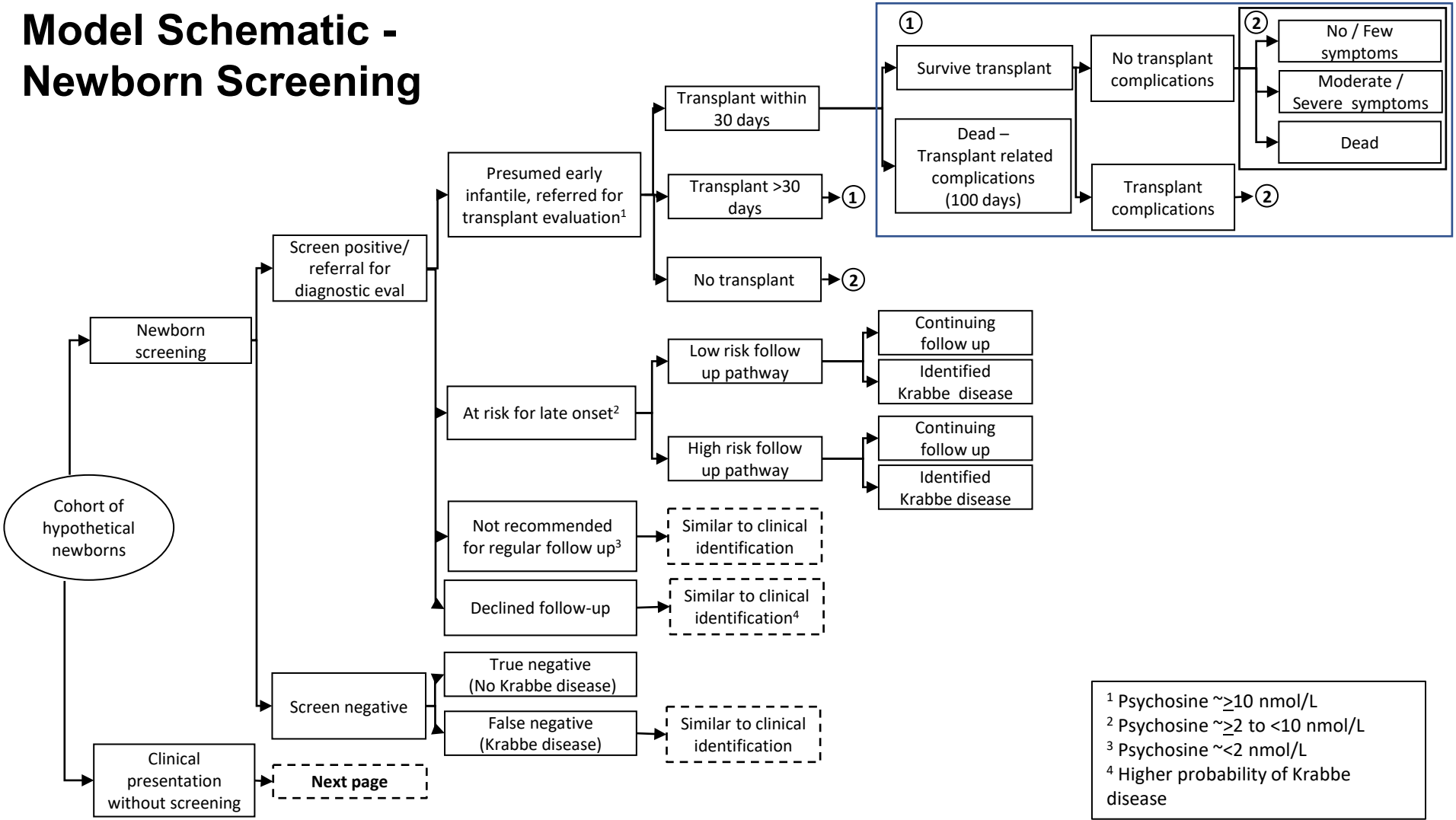
Methodological approach: Decision analysis

- Systematic approach to decision making under conditions of uncertainty
- Project ***ranges*** of short-term outcomes
- Allows decision maker to identify which alternative is expected to yield the most health benefit
- Identify key parameters & assumptions

In Progress

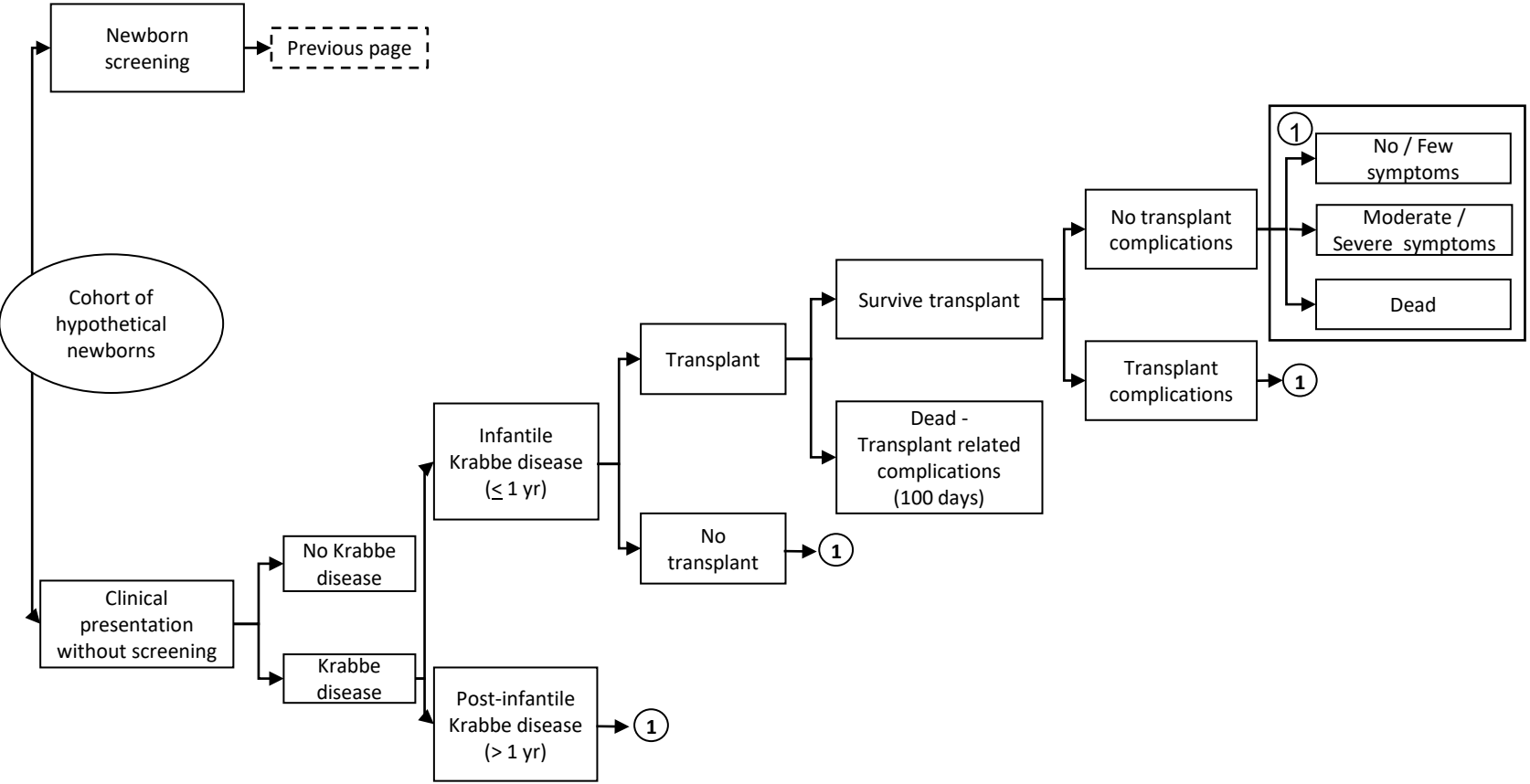
- Model structure in development
- TEP #2 focused on reviewing model structure and assumptions:
  - Time horizon for the modeling analysis: 2-3 years
  - Classification and terminology of screening outcomes
  - Timing of transplant and transplant complications

Model Schematic - Newborn Screening



[1] Psychosine ~≥10 nmol/L
[2] Psychosine ~≥2 to <10 nmol/L
[3] Psychosine ~<2 nmol/L
[4] Higher probability of Krabbe disease

Model Schematic - Clinical Presentation Without Screening



Anticipated results
Table 1. Screening outcomes

Anticipated outcomes with newborn screening for Krabbe Disease	Universal Newborn Screening	Clinical Identification (without universal newborn screening)
Positive screen		
Early onset Krabbe Disease		
At risk for late onset Krabbe Disease		
Low risk follow up pathway		N/A
High risk follow up pathway		N/A
Not recommended for regular follow up		N/A
Declined follow up		N/A

Anticipated results
Table 2. Health outcomes

Anticipated health outcomes for infants diagnosed with Krabbe disease	Universal Newborn Screening	Clinical Identification	Cases or deaths averted
Received transplant			N/A
Projected outcomes @ 3 yrs			
No/few symptoms			
Moderate/severe symptoms			
Dead			

Next Steps

- Iterative process, finalize model structure
- Derive model inputs: data from states with screening programs, literature review, expert panel
- Projected outcomes
- Input/feedback on model structure and outcomes - TEP #3

Public Health Impact Assessment

- Data being collected from the following states offering Krabbe disease newborn screening: Georgia, Illinois, Kentucky, Missouri, New Jersey*,New York, Ohio*, Pennsylvania, Tennessee*

*Interviews completed

Public Health Impact Assessment

- GALC enzyme activity can be measured by MS/MS or fluorometry, and multiplexed with other lysosomal storage disorders screening tests
- Contracted labs are often used to measure psychosine, although it can be done in the state newborn screening lab

Public Health Impact Assessment

- Barriers to implementing newborn screening
  - Staffing
  - Funding
  - Competing priorities
  - Administrative challenges
  - Need to update or change legislation

Public Health Impact Assessment

- Survey of states not offering Krabbe disease newborn screening
  - Webinar held on October 13
  - Survey link distributed end of October

Questions